FINAL SYNOPSIS OF THE LIBBY DENVER EPIDEMIOLOGY MEETING JULY 23-24, 2007

INTRODUCTION AND MEETING GOAL

EPA Region 8, EPA Office of Solid Waste and Emergency Response, and EPA Office of Research and Development convened a meeting in Denver, Colorado on July 23 and 24, 2007 to identify and prioritize new epidemiologic studies and analyses that may contribute information to support an EPA Baseline Risk Assessment for the Libby Montana community.

Meeting participants included scientists, public health assessors, and physicians from EPA, ATSDR, NIOSH, several universities and other institutions, as well as representatives from the Montana Department of Environmental Quality and the Libby community (see Appendix A for a list of meeting attendees).

Initial drafts of this synopsis were prepared by Aubrey Miller of EPA Region 8 (the meeting facilitator and organizer) and Peter McClure and Lynn Woodbury of Syracuse Research Corporation. This final version has been prepared in response to review comments on the initial draft from meeting participants.

SPECIFIC MEETING OBJECTIVES

The following specific objectives were established before the meeting:

- Develop a list of studies or analyses to help address needed areas of investigation with respect to:
    - Clinical course/severity of disease among Libby-amphibole-exposed individuals
    - Susceptible populations
    - Non-pulmonary health endpoints
    - Exposure-response relationships
    - Toxicokinetics and fiber deposition in lung tissue
    - Biomarkers of exposure and disease and genetic studies

- Highlight key requirements associated with suggested studies

- Prioritize potential studies by level of importance and utility in addressing needs

- Identify, for top-tier studies,
    - Key participants and their likely roles
    - Major obstacles to success
    - Action items and next steps necessary to move the analysis or study forward

SUMMARY OF MEETING PROCEEDINGS

1. SYNOPSIS OF PRESENTATIONS OF ONGOING LIBBY SITE-RELATED WORK, RESEARCH, AND INVESTIGATIONS. (MONDAY JULY 23, 2007)

1.1. LIBBY CLEAN-UP EFFORTS: 1999-2006. PAUL PERONARD, U.S. EPA REGION 8

Paul Peronard provided general information about the site location, history, mine characteristics, and mining processes. He summarized the current removal triggers, the clean-up actions that have been performed to date, and the types of environmental sampling and analysis issues that have been encountered. He reminded the group that one of EPA's goals is to better understand non-worker exposures and health effects, because exposures and impacts to vermiculite miners and millers at the Libby site are already well-established. EPA needs to understand the long-term health risks associated with exposures from residual Libby amphibole asbestos contamination in the community. In particular, a primary objective of the ongoing exposure assessment is determining the personal exposures resulting from disturbance of contaminated soils (referred to as the "pig pen effect"). In addition to soil-related exposures, assessments of other pathways are either ongoing or being planned to support a baseline risk assessment for the site and eventually help answer the question of "how clean is clean?".

1.2. MINERALOGICAL CHARACTERISTICS OF LIBBY AMPHIBOLE. GREG MEEKER, U.S. GEOLOGICAL SURVEY

Greg Meeker presented information on the chemical composition and structure of amphibole minerals in general and Libby amphibole, in particular. Amphibole minerals represent a solid solution series of varying chemical compositions of sodium, calcium, magnesium, and potassium at various sites in the crystal structure that determine the type of amphibole (e.g., tremolite, winchite, richterite). Prior to 1978, there were over 200 amphibole names primarily due to slight variations in underlying chemistry. In 1997, the amphibole nomenclature was reduced to 75 categories. Meeker presented scatter diagrams of the chemical compositions for 30 ore samples collected at the Libby mine site showing how different samples fall into naming categories for edenite, tremolite, winchite, richterite, magnesioarfvedsonite, or magnesioribeckite. He also illustrated how differences between the 1978 nomenclature and the current 2004 nomenclature would alter amphibole naming conventions for the Libby ore samples. Plots presenting the relative error associated with calcium and sodium demonstrated the difficulty in making statements regarding amphibole types with certainty. Meeker also presented several examples of the structural morphology for Libby amphibole asbestos, which can range from prismatic to acicular.

1.3. LIBBY ASBESTOS SUPERFUND SITE RISK ASSESSMENT OVERVIEW. WENDY O'BRIEN, U.S. EPA REGION 8

Wendy O'Brien presented a summary of the Superfund remedial process, which includes the Remedial Investigation (RI), the Feasibility Study (FS), the Proposed Plan, the Record of Decision (ROD), and the remedial clean-up. She described how the Baseline Risk Assessment (BRA) helps guide the development and evaluation of remedial approaches for the FS. O'Brien

presented the current conceptual site model (CSM) for human exposures at the Libby site in Operable Unit 4. The CSM includes a variety of potential receptor populations including residents, commercial workers, tradespersons, students/teachers, and recreational visitors. Among the most important asbestos exposure pathways for these receptors are breathing outdoor ambient air, breathing indoor air, and breathing outdoor air near a soil disturbance activity. She described how information about airborne Libby amphibole asbestos exposures during the disturbance of contaminated soils and dusts were being assessed through the performance of staged activities or scenarios, referred to as "activity-based sampling" (ABS). She also described the indoor and outdoor ABS sampling programs that have been conducted in the past and newer activities that are continuing this year (indoor and outdoor ABS sampling) to help quantify the range of exposures resulting from a variety of disturbance scenarios in association with various types of contaminated sources.

1.4. ASBESTOS SAMPLING AND ANALYSIS: CONSIDERATIONS FOR DATA INTERPRETATION. MARY GOLDADE, U.S. EPA REGION 8

Mary Goldade described several of the sampling and analysis challenges that have been encountered at the Libby site. She summarized the air sampling protocols for stationary monitors and personal monitors used in activity-based sampling. Air sample preparation techniques were summarized for Phase Contrast Microscopy (PCM) and Transmission Electron Microscopy (TEM). She also summarized the differences between PCM and TEM. In brief, PCM is relatively cheap and quick to perform, and it is the method that has been used historically. However, PCM is not specific to mineral fibers (i.e., cannot distinguish between asbestos and non-asbestos fibers) and cannot resolve structures thinner than 0.25 um. As a result, PCM has limited value as an analysis method for assessing non-occupational exposures in a community. TEM is better suited for assessing environmental/residential exposures because it has the ability to distinguish asbestos structures from non-asbestos structures and to identify fibers/structures that cannot be observed by PCM. However, TEM is expensive and time-consuming. Goldade highlighted the importance of understanding potential differences in resolution capabilities, and the various TEM counting rules and definitions of structures (e.g., treatment of complex structures) when attempting to make comparisons across data sets.

1.5. EPA/ORD/NHEERL TOXICOLOGY AND DOSIMETRY STUDIES. STEPHEN GAVETT, U.S. EPA/ORD/NHEERL

Steve Gavett summarized the five toxicology and dosimetry studies planned by the National Health and Environmental Effects Research Laboratory (NHEERL) as part of the Libby Toxicity Assessment Action Plan.

- *In Vitro* Dissolution Assays – The goal of this study is to compare the dissolution of various Libby amphibole asbestos samples in acid and synthetic lung lining fluid in order to inform the dosimetry model and toxicity studies.
- *In Vitro* Toxicity Endpoints – The goal of this study is to compare the ability of Libby amphibole asbestos obtained from several sources to cause significant biological effects in cultured cells.

- Comparative Toxicology in Mice and Rats – The goal of this study is to conduct intratracheal instillation animal studies to determine relative potency of Libby amphibole vs. other asbestos types, evaluate respiratory and non-respiratory health endpoints, evaluate potential for increased susceptibility during early life periods, and apply these results to the developing dosimetry model and risk assessment considerations.
- Inhalation Toxicology in Rats – The goal of this study is to compare the toxicity of inhaled Libby amphibole fibers to inhaled positive control fibers (amosite) to determine fiber respirability, deposition and clearance, pathologic changes, and mechanisms of action, and apply these results to the developing dosimetry model and risk assessment considerations.
- Dosimetry Model Development – The goal of this study will be to determine specific dose metrics for accurate response analysis of inhaled Libby amphibole fibers to be able to better predict exposure-response relationships and reduce uncertainties in the human health risk assessment.

Although the focus of these studies will be on comparing Libby amphibole asbestos to negative and positive controls (amosite positive control and wollastonite negative control), other asbestos types may also be evaluated, including amphibole from the El Dorado, California site and chrysotile from the Swift Creek,Washington site. These studies are planned to begin in the third quarter of 2007 and to be completed by the first quarter of 2010. Gavett noted that the topics of animal toxicology, dosimetry, and epidemiology are inter-related and data from each can be utilized to inform each other.

1.6. LIBBY: HEALTH ISSUES AND RISK ASSESSMENT NEEDS. AUBREY MILLER, U.S. PUBLIC HEALTH SERVICE, U.S. EPA REGION 8

Aubrey Miller presented a brief historical overview of the identification of non-cancer and cancer diseases associated with exposure to Libby vermiculite, including the early epidemiological studies of Libby vermiculite workers, and EPA mobilization in 1999 determining that additional health and environmental investigations were necessary for the Libby community. He reviewed the findings that: (1) there is widespread environmental contamination with Libby amphibole asbestos in Libby and elsewhere (e.g., in the vicinity of vermiculite processing plants across the country and in attics with vermiculite insulation materials); (2) there are high rates of disease associated with occupational and non-occupational exposure to Libby amphibole; and (3) there is uncertainty in applying the current EPA guidance for asbestos cancer risk assessment to populations exposed to Libby amphibole (e.g., key exposure-response data sets were mostly for male workers exposed to chrysotile). Miller concluded with the objectives of the current meeting to identify and prioritize new epidemiologic studies and analyses to support the BRA for the Libby community.

1.7. CLINICAL HISTORY OF CASES OF MESOTHELIOMAS AND PLEURAL DISEASE IN LIBBY MONTANA RESIDENTS. ALAN WHITEHOUSE, CLINIC FOR ASBESTOS-RELATED DISEASE (CARD); LIBBY, MT

Alan Whitehouse reported on his clinical experience with Libby residents (vermiculite workers, household contacts of workers, and residents with no known direct, or familial connection to, occupational exposures). He reviewed his observations of the various forms of

pulmonary disease associated with Libby amphibole asbestos exposure. Whitehouse also described several findings from a review of 33 cases of mesothelioma among individuals exposed to Libby amphibole. Whitehouse noted that he has observed about 20 cases, including individuals with occupational and non-occupational exposures who have exhibited unusually rapid progression of pleural disease. He described several cases in which the period between the first detection of pleural abnormalities and the development of severely impaired pulmonary functions or death was relatively short (2 to 6 years). A manuscript describing this case-series is being prepared for publication. It was noted that histopathology and archived lung tissues are not available for previous fatalities; however, information from necropsies for future deaths will likely be available.

1.8. MINING IN LIBBY – HEALTH PERSPECTIVE FROM CRISIS TO CURE. BRAD BLACK, CLINIC FOR ASBESTOS-RELATED DISEASE (CARD); LIBBY, MT

Brad Black presented a brief history of the Zonolite mine and the Libby community. The Center for Asbestos-Related Disease (CARD) was developed in July 2001 to provide pulmonary care and outreach services to meet the special needs of the community in Libby and surrounding areas. Black noted that an important goal of the CARD is to facilitate vigorous and varied research activity in collaboration with multiple institutions, coordinated with ongoing clinical care and medical monitoring of more than 1,800 patients. The CARD has collaborated with multiple individuals and agencies in performing various research efforts including:

- ATSDR, EPA, and Libby Community - Asbestos Screening Program
- ATSDR - CT study of equivocal B-reading results
- ATSDR - Zonolite workers chest x-ray progression study
- New York University - Mesothelioma Applied Research Foundation (MARF) grant for research to investigate biomarkers of asbestos exposure and disease, specifically mesothelioma. Current focus is on serum mesothelin-related protein (SMRP) using blood and urine specimens from individuals living in Libby to provide an external group for validation of this biomarker and future opportunities for early disease detection and treatment. (Point of Contact: Harvey Pass, New York University School of Medicine)
- University of Montana - study of auto-antibodies and single nucleotide polymorphism (SNP) in Libby exposed population
- Montana State University - NIEHS grant for health evaluations of the Libby cohort and increased understanding of health service needs. Data collection will be concluded at the end of September 2007. Montana State University will then do statistical analyses. The expected outcome from this project is a comparison of patient perception of level of well-being with the clinical medical perspective.
- Karmanos Cancer Institute/NCVAC - assist in the development of a CARD database to help understand risk factors for asbestos exposure and disease (see below)
- Karmanos Behavioral Science - community focus group research on cultural values and psychosocial responses to slow motion technological disaster
- ATSDR, NIOSH, and St. John's Hospital - comparison study to evaluate the differences between digital and standard film radiography

Black noted that one of the critical challenges for the CARD is to obtain external funding to maintain continued health care services and sustain the cohesiveness of the patient population for future research and outreach efforts.

1.9. ACTIVITIES OF THE NATIONAL CENTER FOR VERMICULITE AND ASBESTOS-RELATED CANCERS (NCVAC). JOHN GRAFF, KARMANOS CANCER INSTITUTE, WAYNE STATE UNIVERSITY

John Graff presented information on potential exposure of individuals in Michigan to the vermiculite mined in Libby. He noted that asbestos-contaminated vermiculite was shipped from Libby to eight locations in Michigan and that an estimated 800,000+ homes in Michigan have vermiculite attic insulation (VAI). He presented figures that illustrated that incidence of lung cancer and malignant mesothelioma from 1973 to 2002 in the Detroit Tri-county area was higher than U.S. national rates, however it is not known if increased rates are related to VAI.

Graff identified several areas of ongoing NCVAC research and study including:

- Outreach and Communication – The goal is to develop effective communication strategies that influence exposure-related messages, risk communication, procurement of medical evaluations and follow-up, and preventive behavior.
- Early Detection Biomarkers – The goal is to identify patients with asbestos exposure at early stages of disease and analyze expression levels of tumor-associated proteins.
- Asbestos-related Disease Classification – The goal is to validate a new classification system using high-resolution computed tomography (HRCT) and provide online review of CT scans and pulmonary function tests (PFTs).
- Low-Exposure Estimation – The goal is to estimate cumulative asbestos exposure among NCVAC patients (without occupational asbestos exposures) who have VAI in their homes and make recommendations on avoidance of household exposures.
- Detroit Mesothelioma Risk Factor Discovery – The goal is to determine occupational and non-occupational exposure histories of metropolitan Detroit mesothelioma cases.
- Libby Risk Factor Discovery – The goal is to help develop a standardized database of the Libby CARD patients that can be used to evaluate the risk factors of exposure and disease.

Of note: in post-meeting comments Mr. Graff reported that they have already input much clinical information (no survey information) on approximately 300 Karmanos NCVAC clinic patients. No data input has yet begun in Libby, though Karmanos is eager to move forward on this project recognizing that abstraction of existing medical records, patient interviews and consents, and specimen collection are an enormous undertaking given the size of the patient population.

1.10. UPDATING AND REANALYZING NIOSH MORTALITY DATA FOR LIBBY WORKERS. PATRICIA SULLIVAN, NIOSH

Patricia Sullivan presented an overview of her analysis to update and expand the 1980 NIOSH Libby vermiculite worker study (Amandus and colleagues, 1987 Am J Ind Med 11: 1-37). The objectives of the analysis were to:

- add data for about 1,100 workers exposed for <1 year;
- assess mortality data for non-respiratory diseases;
- evaluate exposure-response relationships for non-cancer (i.e., asbestosis mortality) and cancer endpoints; and
- evaluate risk models to develop estimates of risk per unit of exposure (IURs and RfC).

Exposure estimates for these workers (based on PCM counting of structures with length >5 µm) were primarily as described by Amandus and colleagues (1987), along with similar information reported by McDonald et al. (McDonald, JC; McDonald, AD; Armstrong, B; and Sebastien, P. 1986. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Med 43:436-449).

Based on the updated mortality experience, SMRs were calculated for various causes of death (including mesothelioma). Sullivan noted that some of the current SMRs are similar to previous SMRs. A manuscript is being prepared that shows the results of analyses of data for cancer endpoints and non-cancer endpoints, including analysis of exposure-response data for arthritis.

Sullivan also noted that NIOSH still has the B-read results for a cohort of workers (n=184) that underwent chest radiography to evaluate asbestos related pulmonary morbidity (Amandus, HE; Althouse, R; Morgan, WKC; Sargent, EN; and Jones, R. 1987. The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part III. Radiographic findings. Am J Ind Med 11:27-37.)

Sullivan concluded with her assessment of research needs related to health effects associated with Libby amphibole:

- Characterize health risks of non-workers living in Libby;
- Better understand exposures to VAI to construction workers and home owners;
- Obtain fiber size-specific exposure estimates (TEM analysis of historical monitoring samples); and
- Understand mode of action for autoimmune effects associated with exposure to Libby amphibole.

1.11. ANALYSIS OF DISEASE MORBIDITY IN VERMICULITE WORKERS FROM MARYSVILLE OHIO. JIM LOCKEY, UNIVERSITY OF CINCINNATI (UC).

Jim Lockey presented a brief overview of a reexamination of health data for a cohort of 513 people from Marysville, Ohio, site of a vermiculite exfoliation plant. Cumulative exposure estimates for individuals in this cohort were based on individual worker histories and exposures using PCM analysis (counted as structures with lengths >5 µm, diameters <3 µm, and aspect ratios >3:1) of industrial hygiene air samples of various areas in the plant. In the initial cross-sectional health evaluation of this cohort conducted in 1980, about 2% workers in a high-exposure group showed pleural changes in chest radiographs (Lockey, JE; Brooks, SM; Jarabek, AM; Khoury, PR; McKay, RT; Carson, A; et al. 1984. Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite. Am Rev Respir Dis 129:952-958). More

recent follow-up revealed that about 28% had pleural changes. Findings of radiographic pleural disease were also noted to be associated with deficits in pulmonary function. A report of the follow-up is currently in press. Mortality of this cohort is limited (400 of the 513 are still alive) and, therefore, there is limited power to detect elevated specific mortality rates. Exposure-response analysis of the radiographic and pulmonary function data may be useful for deriving an RfC for Libby amphibole. Continued health monitoring of this cohort will be useful to better describe the clinical course of respiratory diseases associated with Libby amphibole.

Another investigation currently being conducted at UC is comparing genomic and proteomic profiles in diseased and non-diseased individuals in the high-exposure group. This analysis may help to identify populations with increased susceptibility for disease from exposure to Libby amphibole.

1.12. U.S. DHHS ACTIVITIES IN LIBBY. VIK KAPIL, U.S. DHHS, ATSDR

Vik Kapil described seven activities related to Libby:

- Libby Medical Screening (2000 and 2001): Data (questionnaire, radiographic B-reader, spirometry) were collected for 7307 individuals from Libby in two phases 2000 and 2001. Spirometric abnormalities among individuals previously screened are being looked at currently. (ATSDR point of contact: Michael Lewin 404 498 0607--- mlewin@cdc.gov)
- MASSA Clinic Screening (2003-present): Data (questionnaire, radiographic B-reader, spirometry) were collected by the Montana Department of Public Health and Human Services for about 2700 individuals from Libby. (ATSDR point of contact: Ted Larson, 404 498 0593 --- thl3@cdc.gov)
- Case Series of Environmental Exposures and Health Effects (2001-2002): Medical records and test results were collected from 22 Libby participants in 2001 and 2002 and reviewed. (ATSDR POC: Dan Middleton, 404 498 0565 --- dcm2@cdc.gov)
- CT Scan Study of Indeterminate Chest X-rays (2001): Data (CT-reader, questionnaire, radiographic B-reader, spirometry) were collected from 353 individuals with indeterminate chest X-rays from the Libby Medical Screening phase 1 (2000). (ATSDR point of contact: Oleg Muranov, 404 498 0562, oim0@cdc.gov)
- Libby Former Mine Worker Chest X-ray Evaluation for Progression of Disease: Radiograph series for 84 Libby workers were evaluated (B-reader data) for progression of disease. (ATSDR POC: Ted Larson, 404 498 0593 --- thl3@cdc.gov)
- Study of Asbestos-related Mortality Among Libby Residents: Currently ongoing analyses of death certificate and NDI data collected for Libby residents (n=TBD). (ATSDR point of contact: Ted Larson, 404 498 0593 --- thl3@cdc.gov)
- National Asbestos Health Evaluation Program (NAHP): Currently ongoing health evaluation of data collected in 2006-2007 for a cohort of vermiculite workers and household contacts (n=TBD) at five Phase 1 sites (Hamilton township, NJ; Santa Ana, CA; Minneapolis, MN; Phoenix, AZ; Glendale, AZ). Data being collected include death certificate, questionnaire, radiographic B-reader, and spirometry data. An initial report is anticipated in 2008. (ATSDR point of contact: Robin Lee 404 498 0605 --- RLee3@cdc.gov).

1.13. LIBBY EPIDEMIOLOGICAL STUDIES. JEAN PFAU, UNIV. OF MONTANA.

Jean Pfau identified four databases that are currently being utilized by the University of Montana to research asbestos-related disease, including:

- Serum – n=275 samples from Libby (CARD) and Missoula AI serology (information on age, gender, diagnosis, and medications provided in questionnaire) (data summarized in Pfau, JC; Sentissi, JJ; Weller, G; and Putnam, EA. 2005. Assessment of autoimmune responses associated with asbestos exposure in Libby, Montana, USA. Environ Health Perspect 113:25-30)
- Blood – n=275 samples from Libby (CARD) and Missoula WBC for DNA & RNA
- Lung lavage – n=12 samples from Libby and Missoula (questionnaire information available)
- Systemic autoimmune diseases (SAID) – n=1,976 samples from Tremolite Asbestos Registry (TAR) with a follow-up survey performed by the University of Montana (data summarized in Noonan, CW; Pfau, JC; Larson, TC; and Spence, MR. 2006. Nested case–control study of autoimmune disease in an asbestos-exposed population. Environ Health Perspect 114:1243-1247)

Current findings show that increasing numbers of systemic autoimmune diseases (SAIDs), rheumatoid arthritis, and lupus cases are directly correlated with the number of asbestos exposure pathways. Pfau described how these datasets were being utilized to better understand the model of initiating events and outcomes in autoimmunity responses. She also summarized results from mouse toxicity studies that have been performed with Korean tremolite and the Libby 6-mix. Efforts to optimize elutriation techniques to generate respirable preparations of these asbestiform materials (to be used in animal toxicity studies) are ongoing. A preliminary report of these efforts is forthcoming (perhaps in August).

1.14. EPA LIBBY CARD DATASYSTEM & DATA INTEGRATION INITIATIVES. MARTIN MCCOMB, U.S. EPA REGION 8

Marty McComb described a process by which: 1) a Libby CARD datasystem could be developed to capture currently available and future health information from the Clinic for research purposes, and 2) a broader-scale datasystem could be developed to enable users to access and integrate currently available clinical, epidemiological, and exposure datasets in order to evaluate health outcomes, assess exposure-response relationships, and conduct future medical research and surveillance. He emphasized that all acquired information would conform to all applicable human subject regulations and medical confidentiality rules and agreements. McComb identified the following tasks in support of this goal:

- Support CARD Clinic, and other entities, necessary to capture historical and prospective clinical information.
- Establish Oversight Board
- Identify Target Datasets
- Establish Technical Team
- Create Exchange Formats and Data Dictionaries
- Publish Exchange Formats to Transaction System
- Develop “Rosetta Stone”
- Create Subscriptions to Transaction System

2. SYNOPSIS OF DISCUSSION OF INVESTIGATIONS TO SUPPORT AND IMPROVE A BASELINE RISK ASSESSMENT FOR LIBBY *USING EXISTING DATA* FOR LIBBY-AMPHIBOLE-ASBESTOS EXPOSED POPULATIONS

(MONDAY AFTERNOON JULY 23 AND TUESDAY MORNING JULY 24)

Following the 14 presentations which reviewed ongoing activities related to understanding the exposures and health effects in vermiculite exposed workers and residents of Libby, Montana, and elsewhere, discussion centered on areas of potential clinical toxicologic and epidemiologic investigations that could help support a baseline risk assessment (BRA) for the Libby community. For each of the areas outlined below, the discussion first centered on potential analyses of **existing data or data-sets** that would help support the BRA. This discussion commenced on Monday afternoon and continued through Tuesday morning. An approximate order of priority (from higher to lower for the analysis of existing data) is indicated by the following presentation order.

2.1. Characterization of Exposure-Response Relationships for Cancer and Non-cancer Health Effects from Exposure to Libby Amphibole: Existing Data

Can we better understand/characterize and quantify the historical exposure-response relationships in both occupationally and non-occupationally Libby-amphibole-asbestos-exposed individuals? Emphasis needs to be placed on risks associated with lower-level exposures and the development of scientifically sound inhalation reference concentration (RfC) and cancer-slope factors (IUR).

The group agreed that analyses of several sets of existing data may be useful to provide a basis for deriving EPA toxicity values for Libby amphibole asbestos (RfC for non-cancer disease, such as interstitial and pleural fibrosis, and Inhalation Unit Risk [IUR] estimates for lung cancer and mesothelioma).

Specific details and timelines for compiling and evaluating the health evaluation and exposure data and conducting the exposure-response analyses were not explicitly discussed.

Of note: In addition to the currently available data, it was felt that additional information concerning health effects associated with non-occupational exposures of those born since 1990 (i.e., after the plant shut down) and post-2000 (after EPA began clean-ups) would need to be obtained during prospective medical surveillance and studies of the Libby population (see Section 3.1).

2.1.1. Existing Datasets Involving *Occupational* Exposures to Libby Amphibole. The group agreed that extrapolation to lower level exposures is a limitation to using the exposure-response data for Libby amphibole-exposed workers to derive EPA cancer and non-cancer toxicity values. This is especially true for former workers in Libby who had high levels of occupational exposure and other exposures by virtue of living in the Libby community. The Marysville cohort was felt to be particularly important and useful with respect to understanding exposure-response relationships, given the lower occupational exposures, availability of follow-up information, and lack of community exposures.

Set 1: NIOSH Study of Mortality and Morbidity in Former Libby Vermiculite Workers

Patricia Sullivan is completing an analysis of the updated mortality and morbidity experience for about 1800 former Libby vermiculite workers. It is expected that the analysis of these data can form the basis for deriving Libby amphibole-specific IURs for lung cancer and mesothelioma. Also, information regarding the exposure-response relationships for non-cancer health endpoints (i.e., interstitial fibrosis (asbestosis), arthritis) and non-pulmonary cancers will be explored.

Set 2: Marysville, Ohio Vermiculite Worker Cohort

Jim Lockey briefly reported on a follow-up evaluation (radiography, pulmonary function variables, questionnaire) on this cohort. A manuscript is currently in press. Analysis of exposure-response data for pleural or pulmonary changes and pulmonary function variables will be very useful for development of an RfC for Libby amphibole for these health endpoints. The mortality experience of this cohort (400/513 are still alive) does not appear to be sufficient for a robust analysis at this time.

Set 3: Western Minerals Worker Cohort – Minnesota

ATSDR sponsored health evaluations (spirometry and radiography) of former Western Mineral workers, household contacts, and community residents exposed to Libby amphibole are ongoing and may be available for analysis next year.

2.1.2. Existing Datasets Involving *Non-occupational* Exposures to Libby Amphibole.

The group agreed that compiling and evaluating existing health evaluation and exposure data for Libby residents without occupational exposures to Libby amphibole could strengthen the development of a non-cancer RfC and cancer IURs for Libby amphibole.

Set 1: Libby Environmental/Residential Non-worker Cohort

Discussion centered on compiling and evaluating exposure and health evaluation data for Libby residents who have not had occupational exposure to Libby amphibole and who would be expected to have experienced lower level exposure than those with occupational exposures. It is expected that analysis of radiographic and pulmonary function data would be useful for developing an RfC for Libby amphibole. If sufficient cases of lung cancer or mesothelioma are identified within this cohort, the data may also be useful for developing IURs for lung cancer and mesothelioma for Libby amphibole.

Useful health evaluation data for individuals to be included in this cohort would include serial chest x-ray and spirometry data and information from questionnaires. Sources of health evaluation data discussed which may be useful for constructing exposure-response data sets include the following:

- Alan Whitehouse's serial radiographic examinations of about 700 Libby residents;
- the Libby CARD Clinic database with information for about 1800 individuals;
- the Libby Medical Screening data (questionnaire, B-reader, and spirometry data) collected in 2000 and 2001 for about 7000 individuals; and
- the MASSA/ATSDR Clinical Screening data (questionnaire, B-reader, and spirometry data) collected since 2003 for about 2700 individuals.

The group agreed that a major challenge will be estimating ("reconstructing") exposures for individuals in this cohort. EPA investigators suggested that environmental exposures can potentially be reconstructed for three time periods: pre-1990, 1990-2000, and post-2000. Elements of this activity will include: using or collecting questionnaire information to estimate pertinent activities of residents; developing reasonable activity-based exposure calculations; analyzing collected indoor and outdoor air samples for their usefulness in activity-based exposure calculations; and applying activity-based exposure calculations to estimate exposures of individuals to be included in the cohort. For indoor (e.g., cleaning, routine activities, home remodeling) and outdoor (e.g., rototilling, mowing, raking, sandbox playing) activities, air samples have been collected and analyzed by EPA Region 8. More of this data collection is planned for this year. W.R. Grace has carried out some air sampling for some other disturbance activities (e.g., pouring a bag of vermiculite in an attic) that may be useful. It may be that individuals may only be able to be categorized into qualitative or semi-quantitative exposure categories (e.g., high, medium, or low). Ambient air samples (collected by EPA Region 8) are much more abundant for the 2000-2007 period than for periods before 2000. There are only a handful of ambient air samples for periods before 2000 (collected by W.R. Grace).

Set 2: Household Contacts of Marysville Workers

Jim Lockey has started a project involving the medical screening of family contacts of former OM Scott workers. As of August 2007, 280 household contacts have agreed to participate in the study out of a goal of 300. Of these 280, 130 have submitted chest radiographs for review. This study will be completed by 2008. Depending on the results, there is a possibility for doing exposure-response analyses and environmental exposure evaluations of former workers homes to determine if residual asbestos is still present, and if so, the nature of any ongoing exposures.

2.2. Special Characteristics of Diseases Associated with Libby Amphibole: Existing Data

Are the clinical courses and severities of non-cancer and cancer diseases being experienced by individuals exposed to Libby amphibole different from those of diseases in individuals exposed to other asbestiform mineral fibers?

The group agreed that Alan Whitehouse's clinical experience and reported observations with Libby patients provides support for the need to collect and analyze information regarding the clinical courses of the health effects associated with exposure to Libby amphibole. Furthermore, other medical experts present at the meeting who have independently reviewed Dr. Whitehouse's findings agreed that there appears to be substantive differences in the severity and progression of asbestos-related disease, and in particular pleural disease, in his patient population compared to personal observations and reports in the medical literature regarding other asbestos-exposed populations. There was general consensus among the participants that the clinical manifestations of disease in the Libby cohort needs to be formally compared to other cohorts exposed to different forms of asbestos materials. Suggestions for comparison populations included: (1) former crocidolite exposed individuals in Wittenoon, Australia; (2) amosite insulation workers being followed by Mt. Sinai Hospital; (3) iron workers being followed by Karmanos Institute; (4) Detroit mesothelioma cases being followed by Karmanos Institute; and (5) former insulation workers in Tyler, Texas.

Existing sources of clinical information that could potentially be prepared and analyzed to assess the clinical course and severity of pulmonary disease associated with exposure to Libby amphibole include:

- Alan Whitehouse's clinical cases and the Libby CARD Clinic (with information for about 1800 individuals, Brad Black, CARD contact)
- the Libby Medical Screening 2000 and 2001 Study (Michael Lewin, ATSDR contact)
- the MASSA (Montana Asbestos Screening and Surveillance Activity) Clinic Screening data collected from 2003 to present (with information for about 2700 individuals; Ted Larson, ATSDR contact; Catherine Le Cour, MDEQ)
- the ATSDR analysis of radiographic B-reader data for 84 Libby vermiculite workers. This study will be evaluating the progression of asbestos-related pulmonary disease among former vermiculite workers in Libby (Ted Larson, ATSDR contact).
    - **Of note:** additional information concerning these workers exposures can help our understanding of the exposure-response relationship & observed findings.
- NIOSH radiographic data on 184 former Libby workers (Patricia Sullivan, contact)
- Marysville, Ohio data on 513 workers with Libby amphibole exposure (Jim Lockey, University of Cincinnati contact)

Specific details for compiling the data and conducting the comparative analysis were not discussed (e.g., who would compile and analyze pertinent descriptive data for cases from Libby, Wittenoon, and insulation workers; what endpoints would be used to characterize and compare the clinical courses; timeline for completion of analysis).

Of note: In addition to the currently available data, it was felt that additional information concerning the special characteristics of disease associated with exposure to Libby amphibole asbestos would need to be obtained during prospective medical surveillance and studies of the Libby population (see Section 3.2).

2.3. Identification of Non-Pulmonary Health Effects Associated with Libby Amphibole: Existing Data

Are individuals in this population experiencing increased adverse health effects secondary to Libby amphibole exposure aside from asbestos-related pulmonary or pleural disease? If so, are such health effects more sensitive to exposure than pulmonary health endpoints?

Sources of existing data to further explore the possibility that non-respiratory health effects may be occurring at elevated frequencies in populations exposed to Libby amphibole include the following:

- the NIOSH mortality and morbidity data set for Libby vermiculite workers (Patricia Sullivan's current analysis of this data set provides some evidence for elevated risk for non-respiratory cancers and arthritis. There may be sufficient data to help characterize exposure-response relationships for these effects in this data set, and address the question of whether or not they occur at lower levels of exposure than those associated with interstitial pulmonary or pleural disease.)

- Alan Whitehouse's clinical experience and records with Libby area residents (Whitehouse noted that there might be an elevated prevalence of sarcoidosis, and that some biopsied tissues may be available for some of the cases.)
- the 2000/2001 Libby Medical Screening, ongoing CARD data set, and MASSA/ATSDR (2003-present) data set.

The nested case-control analysis of the Libby Medical Screening data set by Noonan et al. (Nested case–control study of autoimmune disease in an asbestos-exposed population. 2006. Environ Health Perspect 114:1243-1247) found elevated odds ratios for having one of three (SAIDs (systemic lupus erythematosus, scleroderma, or rheumatoid arthritis) and for having rheumatoid arthritis among those ≥65 years of age who had occupational exposure to Libby vermiculite. Also found was evidence for increasing risk for SAIDs with increasing value for a crude index of exposure (numbers of experienced vermiculite exposure pathways). Refinements on exposure estimates and analysis of the CARD and MASSA/ATSDR Clinical Screening data sets may help to more clearly establish the association between exposure to Libby amphibole and SAIDs, and to characterize exposure-response relationships.

Of note: In addition to the currently available data, it was felt that additional information concerning non-pulmonary health endpoints would need to be obtained during prospective medical surveillance and studies of the Libby population (see Section 3.4).

2.4. Identification of Susceptible Populations, Fiber Toxicokinetics, Lung Fiber Burden, or Biomarker Information: Existing Data

Meeting participants also considered whether there was any substantive data currently available to address EPA concerns regarding:

- Libby amphiboles asbestos exposure to susceptible populations (including genetic predisposition for disease),
- the toxicokinetics and deposition of asbestos fibers in lung tissue, and
- useful biomarkers for Libby amphibole asbestos exposure or disease.

It was felt that the currently available data was not sufficient to address issues or concerns for these areas with respect BRA objectives and that additional information would need to be obtained during prospective medical surveillance and studies of the Libby population (see Section 3).

3. SYNOPSIS OF INVESTIGATIONS REQUIRING NEW EFFORTS OR NEW DATA COLLECTION FROM LIBBY-AMPHIBOLE-EXPOSED POPULATIONS (TUESDAY AFTERNOON JULY 24)

On Tuesday afternoon, the discussion focused on various options for the collection and analysis of **new data** that would help support the BRA for each of the areas outlined below.

As part of the discussion several participants raised the issue of privacy and confidentiality (regarding personal identifiers) and HIPAA issues related to sharing clinical data and ownership of the datasets. The group recognized this as an important concern that would need to be addressed. At the meeting, there was some discussion of an "oversight committee" to handle these issues. Any study using existing or new data must receive Institutional Review Board (IRB) approval to ensure the protection of study subjects' rights and maintain the confidentiality of health information. HIPAA issues would also have to be resolved. If an oversight committee is established, it needs to include those with expertise in these areas. In addition, the issue of ownership of the dataset must be resolved prior to conducting any studies.

3.1. Characterization of Exposure-Response Relationships for Cancer & Noncancer Health Effects Among the Libby Community: New Data

Prospective health evaluations of non-occupationally exposed individuals living or born in Libby, especially since 1990, may provide useful exposure-response data for cancer and non-cancer health effects if reasonable measures of exposure can be developed to accompany collected health status data. To improve understanding of individual's experiences with differing exposure pathways, surveys should be conducted to collect pertinent information about behaviors and activities (i.e., frequency and duration) with regard to the exposure pathways of concern.

Useful health status data (collected serially) could include CT scans, chest x-rays, full pulmonary function testing (i.e., spirometry, lung volumes, diffusion capacity, lung compliance testing), pulmonary exercise stress testing, and symptom/health status questionnaire information. Periodic collection of standardized health status data can also provide critical information about the clinical course of disease in this population, risks for potentially susceptible groups (i.e., early life exposures), possible associations between exposure and non-pulmonary health effects, such as SAIDs, and psychosocial/quality of life issues associated with asbestos-related illnesses. Further, the collection and storage of biological specimens (e.g., blood, urine, nasal or bronchial lavage fluid, sputum, or lung tissue) from individuals with specified exposures or diseases will be useful to verify/validate: (1) exposure estimates, when, and if, more reliable biomarkers of exposure are developed; or (2) health effects, when, and if, pertinent biomarkers of specific effects (either respiratory or non-respiratory) are developed (as is currently being pursued through joint research by the CARD Clinic, Karmanos Institute, and New York University School of Medicine).

Sources of available health status data discussed that may be useful as a foundation to support new prospective medical surveillance and investigations to improve our understanding of exposure-response relationships post-2000 include:

- Alan Whitehouse's serial radiographic examinations of about 700 Libby residents;

- the Libby CARD Clinic database with information for about 1800 individuals
- the Libby Medical Screening data (questionnaire, B-reader, and spirometry data) collected in 2000 and 2001 for about 7000 individuals; and
- the MASSA/ATSDR Clinical Screening data (questionnaire, B-reader, and spirometry data) collected since 2003 for about 2700 individuals.

3.2. Special Characteristics of Diseases Associated with Libby Amphibole: New Data

Prospective health evaluations of non-occupationally exposed individuals living or born in Libby since 2000 also will provide useful information to augment the analyses of existing data on the clinical course and progression of diseases in Libby-amphibole-exposed subjects in comparison with progression of diseases in populations exposed to other asbestiform materials (see Section 2.2). Health status data to be collected serially and used to describe the disease progression would be the same as those described in Section 3.1 (including the biological specimens which may be useful in the future to verify exposure or effects).

3.3. Identification of Subpopulations Susceptible to Libby Amphibole: New Data

Do individuals who are exposed in childhood or who have other illnesses (i.e., autoimmune disease, other pulmonary disease, other illnesses) have increased risk for asbestos-related disease in this population?

Discussion of the issue of possible childhood susceptibility centered around the possible usefulness of data (questionnaire data and some radiographic and spirometry data) for about 600 individuals from the 2000-2001 Libby Medical Screening data set who were between the ages of 10 and 18 years (about 8% of the total of about 7000 individuals including in the screening), coupled with information in the CARD or MASSA/ATSDR data sets. Analysis of these data may be useful for discerning patterns or trends for childhood susceptibility, "familial" sensitivity, and correlations with other conditions (e.g., autoimmune disease, asthma, smoking, and passive smoking). Inclusion of these individuals in prospective medical surveillance investigations will provide additional information for discerning these possible patterns or trends.

3.4. Identification of Non-pulmonary Health Effects Associated with Libby Amphibole: New Data

With the proper design of the health status questionnaire, prospective health evaluations of non-occupationally exposed individuals living or born in Libby since 2000 can provide information to further investigate the possible association between exposure to Libby amphibole and increased risk for SAIDs or other non-pulmonary health endpoints. Identification of other health endpoints of concern, in this situation asbestos exposure-sensitive non-pulmonary health endpoints, is a required element of consideration for EPA risk assessments; for the Libby site such information will help to reduce uncertainty around risk estimates developed during the Baseline Risk Assessment.

3.5. Toxicokinetics and Fiber Deposition in Lung Tissue: New Data

The evaluation of lung tissue specimens was discussed with respect to improving our understanding of exposure (lung tissue fiber burden) among community members with varying exposures, the associated lung disease, and the extent and location of fiber deposition and

pathology to support development of human asbestos dosimetry models for Libby amphibole exposure. The utility of lung burden studies in helping to reduce uncertainty with respect to more recent and ongoing community exposures and to support the development of exposure-response models for use in a Baseline Risk Assessment was also discussed. Only a few lung tissue samples have been collected and stored for individuals exposed to Libby amphibole. Further investigation regarding these, and other samples to be acquired, is pending. It may be useful to establish agreements to obtain lung tissue (after death) from Libby-area individuals in a prospective health surveillance investigation.

NOTE: ATSDR submitted the following post-meeting comment. "While ATSDR recognizes research opportunities that banked lung tissue samples may offer, it is impossible to translate information on lung fiber content to past exposures, and it's not known whether lung fiber content would be an appropriate descriptor for predicting diseases occurring in other tissues, such as mesothelioma. It is unclear how collecting these tissues will contribute to developing the Baseline Risk Assessment or making other cleanup decisions."

3.6. Identification of Biomarkers of Exposure and Disease and Genetic Studies: New Data

3.6.1. ATSDR 2006 Expert Panel

In discussing the identification of biomarkers of Libby amphibole exposure and disease and the available data that may identify useful biomarkers, several references were made to the ATSDR (2006) *Report on the Expert Panel on Biomarkers of Asbestos Exposure and Disease*. The purpose of the panel was to discuss the feasibility and state of the science in using various biomarkers to assess recent community exposure to asbestos. The general findings of the panel as summarized in the Executive Summary follow:

> The panelists agreed that the most promising techniques for determining recent environmental asbestos exposure were (1) analyzing lung tissue collected from young people at autopsy and (2) determining fiber content from BAL fluid of carefully selected subjects. They also commented that determining fiber content from sputum samples and blood tests such as mesothelin and osteopontin could prove to be useful in the future, but not without some additional research.
>
> For a variety of reasons, the majority of the panelists did not recommend the following techniques: (1) collecting lung tissue from living humans, (2) using fiber analysis techniques in sentinel animals, (3) as a sole measure, counting asbestos bodies in human tissue, BAL fluid, and sputum, (4) assessing lung function with clinical tests such as spirometry, and (5) for recent exposures, evaluating for pleural or parenchymal changes in chest x-rays and CT scans.
>
> (The entire report, as well as verbatim transcripts of the proceedings, is available at http://www.atsdr.cdc.gov/asbestos/asbestos/biomarkers_asbestos/).

3.6.2. Fibers in Urine

The discussion also focused on the possibility of using urine for a biomarker of exposure. Philip Cook wrote a review (1983. Review of published studies on gut penetration by ingested

asbestos fibers. Environ Health Perspect 53:121-130) of the published evidence for and against gut penetration and tissue accumulation of ingested mineral fibers. The review focused only on reports on the detection of fibers in tissues or fluids in animals or human subjects who were orally exposed to mineral fibers, without inhalation exposure. Among the 19 reviewed studies, the 5 studies noted below analyzed urine for the presence of fibers.

1. Cook, PM; and Olson, GF. 1979. Ingested mineral fibers: elimination in human urine. Science 204:195-198.
2. Hallenbeck, WH; and Patel-Mandlik, KJ. 1979. Presence of fibers in the urine of a baboon gavaged with chrysotile asbestos. Environ Res 20:335-340.
3. Cook, PM; and Longrie, DL. 1980. Determination of asbestos and other inorganic particle concentrations in urine. In: Russell, PA, ed. Electron microscopy and x-ray applications to environmental occupational health analysis, II. Ann Arbor MI: Ann Arbor Science Publishers, Inc.; pp. 219-231.
4. Bingo, J; Sebastian, P; Gaudi Chet, A; and Garand, MC. 1980. Biological effects of attapulgite. In: Wagner, JC, ed. Biological effects of mineral fibers, IARC Sci Publ No. 30. Vol. 1; pp. 163-189.
5. Hallenbeck, WH; Markey, DR; and Dolan, DG. 1981. Analysis of tissue, blood, and urine samples from a baboon gavaged with chrysotile and crocidolite asbestos. Environ Res 25:349-360.

The review concluded that a very small fraction of ingested fibers penetrates the gastrointestinal tract (Cook, 1983). For example, amphibole fiber concentrations in human urine samples were about a thousand-fold less than the concentrations of the same fibers in drinking water consumed by the subjects for up to 20 years prior to the sample collections (Cook and Olson, 1979). However, the results presented by Cook and Olson (1979) suggest that there may be some link between levels in urine and exposure levels. Urine samples from two previously exposed individuals who drank filtered water for 2 or 13 months showed ≥90% reduction in amphibole concentration, compared with urine concentrations before switching to filtered water. Other studies suggest that levels of fibers in urine may not be a reliable biomarker of exposure. For example, preliminary analysis of urinary fiber concentration data for six workers exposed to chrysotile and six non-exposed subjects found that although levels in exposed workers were greater than those in non-exposed subjects, a correlation did not exist between urinary and airborne asbestos concentrations (Finn, MB; and Hallenbeck, WH. 1984. Detection of chrysotile asbestos in workers' urine. Am Ind Hyg Assoc J 45:752-759).

3.6.3. Collection of Biological Samples

The availability of biological samples from individuals exposed to Libby amphibole was discussed. Harvey Pass at NYU has a set of frozen samples (n=300-500) of serum, plasma, and urine from individuals with a range of expected exposures to Libby amphibole; these samples will be used to evaluate and validate new biomarkers found to be associated with mesotheliomas (e.g., SMRP, osteopontin). The Montana CARD and Karmanos Cancer Institute have collected biological samples from patients that may be useful for biomarker development or future estimations of past exposure.

The stored biological samples from Libby amphibole-exposed individuals may be useful for future studies on genomic and proteomic profiles and the identification of biomarkers of susceptibility associated with genetic or gene expression differences. The University of Cincinnati has an ongoing research project examining genomic and proteomic patterns in diseased and non-diseased members of the high-exposure group in the Marysville, Ohio vermiculite worker cohort. The possible usefulness of future investigations of a similar nature with biological samples from other groups of individuals with exposure to Libby amphibole was discussed (e.g., the subgroup of individuals in the 2000-2001 Libby Medical Screening who were between 10 and 18 years of age). Future studies of genomic and proteomic patterns in individuals of various exposure categories with and without disease may be useful in better understanding susceptibility to diseases associated with Libby amphibole.

APPENDIX A
LIST OF MEETING PARTICIPANTS

Brad Black	Libby CARD Clinic
Ron Dodson	ERI Consulting
John Graff	Karmanos Cancer Institute Wayne State University
Michael Harbut	Karmanos Cancer Institute Wayne State University
Gerry Henningsen	H and H Scientific Services, Technical Advisor, Libby TAG
Aparna Koppikar	U.S. EPA (retired)
Richard Lemen	U.S. Assistant Surgeon General (retired)
Stephen Levin	Mt. Sinai Hospital
James Lockey	University of Cincinnati
Jean Pfau	University of Montana
Leroy Thom	Libby ARD Board
Alan Whitehouse	Libby CARD Clinic
Frank Bove	ATSDR
Jill Dyken	ATSDR
Vik Kapil	ATSDR
Glen Tucker	ATSDR
Patricia Sullivan	NIOSH
Ralph Zumwalde	NIOSH
Greg Meeker	USGS
Catherine LeCours	Montana Department of Environmental Quality
Douglas Ammon	U.S. EPA OSWER
Thomas Bateson	U.S. EPA ORD NCEA
Philip Cook	U.S. EPA ORD NCEA MCED
Danielle Devoney	U.S. EPA ORD NCEA
Stephen Gavett	U.S. EPA ORD NHEERL
William Sette	U.S. EPA OSWER
Bob Sonawane	U.S. EPA ORD NCEA
Brad Venner	U.S. EPA NEIC
Pamela Williams	U.S. EPA ORD
Mary Goldade	U.S. EPA Region 8
Jim Luey	U.S. EPA Region 8
Martin McComb	U.S. EPA Region 8
Aubrey Miller	U.S. EPA Region 8
Wendy Obrien	U.S. EPA Region 8
Paul Peronard	U.S. EPA Region 8
Peter McClure	Syracuse Research Corporation
Lynn Woodbury	Syracuse Research Corporation